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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/537,859	03/28/2000	Paul Proost	49673	5520

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

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23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/537,859	Applicant(s) PROOST ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. The request filed on 1/22/03 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/537,859 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's amendment, filed 1/22/03 (Paper No. 22), is acknowledged.
Claims 13-23 have been cancelled. Claims 1-12 have been cancelled previously.
Claims 24-30 have been added.
Claims 24-30 are pending and under consideration in the instant application.

It is noted that Applicant's request to amend line 30 of page 6 (Figure 1 description) HAS NOT BEEN ENTERED as the request does not comply with 37 CFR 1.121(b).

Drawings

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
It is noted that required drawing changes are no longer being held in abeyance by the Office.
Please see the form PTO-948 previously provided as part of Paper No. 11.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES
Correction of Informalities -- 37 CFR 1.85
New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. *The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.*

Timing of Corrections
*Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.*

Sequence Compliance

4. Sequence compliance: Applicant's provision of a corrected CRF, Sequence Listing, and Statement that the contents are identical on 1/22/03, is acknowledged. The CRF has been found acceptable and entered. However, see the comments below regarding New Matter which indicate that a replacement Sequence Listing will be required.

Objections to the Specification

5. The amendment filed 1/22/03 (Paper No. 22), is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The Sequence Listing provided 1/22/03 includes SEQ ID NO:4. SEQ ID NO:4 does not appear in the specification or Figures and thus is New Matter added to the specification. SEQ ID NO:4 differs from the position 6-76 sequence of MCP-2 at position 41 of SEQ ID NO:4, and the MCP-2 variant at positions 39 and 41 of SEQ ID NO:4.

Applicant is required to cancel the New Matter in the reply to this Office action.

Priority

6. Receipt is again acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Application 97116863.8 filed in Europe on 9/29/97; application 97122471.2 filed in Europe on 12/19/97; and application 98104216.1 filed in Europe on 3/10/98 each appear to provide adequate written support for a truncated form of MCP-2 lacking residues 1-5 (that is, "MCP-2 (6-76)") and a mature MCP-2 protein comprising 76 amino acids ("MCP-2 (1-76)").

In addition, each of the priority documents appears to provide adequate written support for an MCP-2 protein missing "up to 5" amino terminal amino acids.

However, the "variant" MCP-2 sequence presented in SEQ ID NO:5 (the lower sequence of Figure 1), does not appear to have support in any of the priority documents.

Thus the effective filing date of instant claims 27-30, encompassing the variant MCP-2 sequence, is considered to be September 28, 1998. Instant claims 24-26 do appear to have an effective filing date of September 29, 1997.

7. This Office Action will be in response to applicant's arguments, filed 1/22/03 (Paper No. 22). The rejections of record can be found in the previous Office Action (Paper No. 16).

It is noted that New Grounds of Rejection are set forth herein.

8. Applicant's cancellation of claims 13-23 has obviated the previous objections and rejections with respect to these claims.

9. It is noted that the instant Sequence Listing clearly sets forth a leader peptide in SEQ ID NOS:2 and 5 by providing negative numbering. Thus the reference to, e.g., positions 6-76 of SEQ ID NO:2, is found to unambiguously indicate that the sequence encompasses, e.g., positions 6-76 of the mature MCP-2 polypeptide.

10. In view of the instant claim language which excludes truncation of the N-terminus beyond those residues identified, Rollins et al. (US Pat. No. 5,739,103, of record) does not appear to anticipate the instant claims.

Claim Rejections - 35 U.S.C. § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 24-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Damme et al. (J. Exp. Med. 1992;176:59-65, IDS #AM) in view of Gong et al. (J. Exp. Med. 1995;181:631-640, IDS AP), and in further view of Van Coillie et al. (Biochem Biophys. Res. Com. March 1997;231:726-730, IDS #AS).

Applicant's arguments, filed 1/22/03, have been fully considered but have not been found convincing.

Applicant argues that Gong et al. provide no reasonable expectation that the instantly claimed truncations would function as chemokine antagonists. Applicant argues that Gong et al. show that the truncation which removed fewer amino acids (i.e. a RANTES 6-68 polypeptide) produced the least displacement compared to the other truncations (e.g., RANTES 9-68). Applicant concludes that based on the teachings of Gong et al. that truncation of 5 amino acids from the amino terminus (i.e., RANTES 6-68) are less effective at displacement than the truncations of more amino acids, the ordinary artisan would not have been motivated to produce truncations involving only amino acid residue 1, 1-2, 1-3, or 1-4.

Applicant's arguments are addressed below as applied to the amended claims.

The instant claims are drawn to amino-terminally truncated MCP-2, lacking NH2-terminal amino acids corresponding to amino acid residues 1, 1-2, 1-3, or 1-4 (MCP-2 2-76, MCP-2 3-76, MCP-2 4-76 and MCP-2 5-76) having antagonistic activity, and pharmaceutical compositions thereof.

As previously noted, Van Damme et al. teach the purification and characterization of MCP-2 as a C-C chemokine structurally and functionally homologous to MCP-1 and MCP-3 (see entire document). Van Damme et al. show that MCP-2, like MCP-1 and MCP-3, induces monocyte chemotaxis both *in vitro* and *in vivo* (e.g. pages 61-62).

Van Damme et al. do not teach amino terminally truncated MCP-2 polypeptides that have chemokine antagonistic activity.

Gong et al. teach that amino-terminal truncations of the chemokine MCP-1 have chemokine antagonistic activity (see entire document, e.g., Abstract). In addition, Gong et al. teach a broadly applicable method of identifying chemokine antagonists by progressively shortening the amino terminus of MCP-1, then screening for receptor binding and inhibition of responses to the intact chemokine (see entire document, especially Figure 8 and Discussion). Gong et al. also teach that chemokine receptor antagonists can be used therapeutically to block monocyte infiltration, a key early factor in a number of allergic and chronic inflammatory diseases (summarized on page 631); and conclude that truncation of the amino terminus of MCP-1 provides a means for generating such antagonists (see concluding remarks on page 638).

Van Coillie et al. teach that there are two alleles of MCP-2 that differ at position 46: one allele encodes a Lys, while the other encodes a Gln (see entire document, especially the sequence of Figure 1). The difference between SEQ ID NO:2 and SEQ ID NO:5 of the instant claims is this allelic polymorphism.

The Examiner has previously argued that given the teachings of Van Damme et al. that MCP-2 is a structural and functional equivalent of MCP-1, the ordinary artisan at the time the invention was made would have been motivated to apply the production and screening of progressive amino terminal deletions approach used by Gong et al. to develop MCP-1 antagonists, to also develop antagonistic amino terminal truncations of MCP-2. Since both MCP-2 and MCP-1 recruit monocytes which are important in a variety of inflammatory conditions; the ordinary artisan at the time the invention was made would have been motivated to produce and screen multiple amino-terminal truncations of MCP-2 in order to identify an antagonist of MCP-2 that could be substituted or combined with antagonists of MCP-1 to better inhibit monocyte recruitment in those inflammatory conditions.

Contrary to Applicant's assertions noted supra, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the instantly claimed. Gong et al. provide a screening approach for identifying antagonists. Van Damme et al. establish that MCP-1 and MCP-2 have similar structures and functions. Thus the ordinary artisan at the time the invention was made would have had a reasonable expectation that amino terminal truncations of MCP-2 would, like amino terminal truncations of MCP-1, function as antagonists.

Applicant's comment regarding RANTES truncations are acknowledged. However, Gong et al. teach the production and screening of progressive truncations of the amino terminus. Thus even though some truncations might be better antagonists than others, the approach taught by Gong et al., using a structurally and functionally related chemokine MCP-1, would have motivated the ordinary artisan at the time the invention was made to make a series of truncations that would have included those recited in the instant claims. In addition, that fact that there was variation in the potency of the different truncations of MCP-1 would further motivated the ordinary artisan to make a series of MCP-2 amino terminal

truncations that systematically progressive removed additional amino acids so that the best antagonist could be identified.

Further, the ordinary artisan would have been motivated to provide pharmaceutical compositions comprising any such antagonists in order to evaluate their relative efficacy in various in vitro assays and disease models of inflammation; and would have had a reasonable expectation of successfully utilizing an MCP-2 antagonistic pharmaceutical composition in inhibiting at least some models of inflammation. Finally, glycosylated forms of the amino-terminally truncated MCP-2 antagonistic proteins would be produced as a consequence of the expression systems that the ordinary artisan would utilize in order to produce sufficient quantities of the truncated MCP-2.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as it applies to the instant claims.

13. Claims 24-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rollins et al. (U.S. Pat. No. 5,739,103, of record) in view of Van Damme et al. (J. Exp. Med. 1992;176:59-65, IDS #AM) and in further view of Van Coillie et al. (Biochem Biophys. Res. Com. March 1997;231:726-730, IDS #AS).

The instant claims are drawn to amino-terminally truncated MCP-2, lacking NH2-terminal amino acids corresponding to amino acid residues 1, 1-2, 1-3, or 1-4 (MCP-2 2-76, MCP-2 3-76, MCP-2 4-76 and MCP-2 5-76) having antagonistic activity, and pharmaceutical compositions thereof.

Rollins et al. teach and claim amino-terminally truncated chemokines having antagonistic activity, including MCP-2; and methods comprising administering amino-terminally truncated chemokines including MCP-2, for inhibition of chemotaxis of various cellular populations in various diseases (see entire document, especially column 1 at lines 59-62, column 3, columns 6-8, and the claims).

The amino-terminally truncated MCP-2 taught by Rollins et al. include truncations that are "about 1 to about 10 or about 2 to about 7" of the endogenous chemokine sequence (see e.g., column 3, especially lines 18-34, and claims).

Rollins et al. teach assays for identifying truncations of chemokines that are antagonistic by exemplifying identification of the related chemokine MCP-1 antagonists (see e.g., columns 9-11).

In addition, Rollins et al. teach recombinant production of amino-terminally truncated chemokines in eukaryotic cells, which would inherently result in a glycosylated protein (e.g., column 8, especially lines 11-20). Finally, Rollins et al. teach the formulation of the amino-terminally truncated MCP-2 in a pharmaceutically acceptable carrier for administration to a patient for treatment of a MCP-2-mediated disease (e.g. columns 6-7).

Rollins et al. do not explicitly teach truncations of MCP-2 that are MCP-2 2-76, MCP-2 3-76, MCP-2 4-76 and MCP-2 5-76.

However, these species are encompassed by the small genus of truncations which are explicitly taught and claimed by Rollins et al. (i.e., truncations involving about 1 to about 10 amino terminal amino acids).

As previously noted, Van Damme et al. teach the purification and characterization of MCP-2 as a C-C chemokine structurally and functionally homologous to MCP-1 and MCP-3 (see entire document). Van Damme et al. show that MCP-2, like MCP-1 and MCP-3, induces monocyte chemotaxis both *in vitro* and *in vivo* (e.g. pages 61-62).

Van Coillie et al. teach that there are two alleles of MCP-2 that differ at position 46: one allele encodes a Lys, while the other encodes a Gln (see entire document, especially the sequence of Figure 1). The difference between SEQ ID NO:2 and SEQ ID NO:5 of the instant claims is this allelic polymorphism.

Rollins et al. provide a general teaching with respect to the production of chemokine antagonists via truncation of amino acids at the amino terminus of any of several chemokines, including MCP-2 and exemplifying MCP-1; and Van Damme et al. establish that MCP-2 and MCP-1 are structurally and functionally related.

Rollins et al. provide clear guidance to delete amino acids from position 1 to position 10 of the amino terminus of the chemokines taught, including MCP-2.

Rollins et al. teach a small genus of amino terminal truncations of chemokines including MCP-2, but does not reduce to practice or explicitly list the members of this genus.

The ordinary artisan would have been motivated to produce the instantly recited truncations of MCP-2 as part of the routine optimization and screening of the small genus of truncations taught by Rollins et al. The ordinary artisan at the time the invention was made would have been motivated to make the instantly recited truncations of MCP-2 and formulate them in pharmaceutically acceptable carriers in order to compare the relative potency of each member of the small genus taught by Rollins et al. as antagonists in models of inflammation; and thereby identify the most potent antagonist.

Both Rollins et al. and Van Damme et al. recognized that both MCP-2 and MCP-1 recruit monocytes which are important in a variety of inflammatory conditions; thus the ordinary artisan at the time the invention was made would have been motivated to produce and screen multiple amino-terminal truncations of MCP-2 in order to identify an antagonist of MCP-2 that could be substituted or combined with antagonists of MCP-1, as exemplified by Rollins et al., to better inhibit monocyte recruitment in those inflammatory conditions.

Given the teachings by Rollins et al., the ordinary artisan at the time the invention was made would have had a reasonable expectation that most, if not all, members of the genus taught by Rollins et al. would function as antagonists. Further, given the guidance provided by Rollins et al. as to how to make and screen for MCP-2 antagonists; the ordinary artisan at the time the invention was made would have had a reasonable expectation of making the instantly claimed truncations in glycosylated form. Thus the ordinary artisan at the time the invention was made would have found it obvious to make the MCP-2 2-76, MCP-2 3-76, MCP-2 4-76 and MCP-2 5-76 truncations of either MCP-2 allele recited in the instant claims.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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March 27, 2003

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3/27/03